

EFFECT OF STRESS HYPERGLYCEMIA, IN ACUTE ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

Background

Stress hyperglycemia, after an acute myocardial infarction may be associated with increased risk of heart failure, cardiogenic shock, and death.

Objectives

- *To study the effect of stress hyperglycemia, on the development of cardiogenic shock, heart failure, arrhythmia and death*
- *To determine, whether the site of myocardial infarction has an effect on development of stress hyperglycemia*
- *To determine, whether this hyperglycemia occurs more in patients, who receive thrombolytic therapy or in those who do not receive it.*

Patients and methods

This study had enrolled 92 patients, with acute ST elevation myocardial infarction, who had no history of diabetes or heart failure, who were consecutively admitted to (emergency department then to CCU and medical ward) in Baghdad Teaching Hospital, during the period of one year between 1st of December, 2011 to 1st of December, 2012.

All of the patients had been thoroughly examined and sent for random plasma glucose and HbA1c; in addition ECG, cTn and echo cardiographic examination had been made, for all of them. Statistical analysis had been done, using student's T-test and Chi square test, according to the type of data to analyse. P value <0.05 had been selected as level of statistically significant association or difference.

Results

A total number of 92 patients were studied; Group 1: 60 patients (60%) were normoglycemics, along their hospital admission.

Group 2: 32 patients(32%) were hyperglycemics, due to myocardial infarction induced stress. 8 patients (8%) were excluded from the study because, their HbA1c was elevated (they were considered undiagnosed DM).

The incidence of heart failure, cardiogenic shock and death were high in group 2. While, the incidence of cardiac arrhythmias is not significantly differed between group 1 and group 2 patients.

Extensive myocardial infarction occurred more frequent in group 2 patients.

Conclusions

- *Stress hyperglycemia, is independently a poor prognostic factor in acute ST elevation myocardial infarction; it*

is independently associated with increased incidence of heart failure, cardiogenic shock and death.

- *Patients with extensive myocardial infarction are more liable, to get stress hyperglycemia.*
- *Stress hyperglycemia is not associated with increased incidence of cardiac arrhythmia.*
- *Stress hyperglycemia occurs more in patients, who receive thrombolytic therapy.*

KEYWORDS: Stress Hyperglycemia & Acute ST Elevation Myocardial Infarction

Received: Aug 31, 2017, **Accepted:** Sep 20, 2017, **Published:** Nov 02, 2017, **Paper Id:** IJMPSEDEC20171

INTRODUCTION

Acute Myocardial Infarction

Pathophysiology

Acute coronary thrombosis, resulting in total occlusion of a coronary artery, leads to ST-segment elevation myocardial infarction (STEMI) (1). Exposure of the lipid-rich core, after atherosclerosis plaque rupture/erosion into the arterial lumen triggers the formation of unstable platelet aggregates, which may lead to intermittent reduction in coronary flow and cause distal embolization (2).

There are two basic types of acute myocardial infarction, based on pathology:

- **Transmural:** associated with atherosclerosis, involving a major coronary artery. It can be sub classified into anterior, posterior, inferior, lateral or septal. Transmural infarcts extend, through the whole thickness of the heart muscle and are usually a result of complete occlusion of the area's blood supply. (3) In addition, on ECG, ST elevation and Q waves are seen.
- **Subendocardial:** involving a small area in the subendocardial wall of the left ventricle, ventricular septum, or papillary muscles. The subendocardial area is particularly susceptible to ischemia. (4)

Risk Stratification

Risk stratification of patients with STEMI can be based on physical examination findings at the time of presentation. The Killip classification is easy to use and provides a rapid method of risk-stratifying patients, in the emergency department, although the mortality rates may overestimate those in the modern era). (5)

Table: Killip Classification for Patients with STEMI (5)

Killip Class	Hospital Mortality (%)
I. No congestive heart failure	6
II. Mild congestive heart failure, rales, S3 congestion on chest radiograph	17
III. Pulmonary edema	38
IV. Cardiogenic shock	81

Diagnosis

Clinical Presentation

The classic symptom of AMI is central substernal chest discomfort, that may radiate to the neck, back, or arms.

The discomfort is persistent (unrelieved by rest or nitrates); is frequently associated with diaphoresis, nausea, dyspnea, and fear of impending death; and usually achieves maximum intensity over several minutes, at least 20% of patients with AMI, however, may lack classic chest discomfort and instead have atypical symptoms(6).

Electrocardiographic Manifestations

All patients presenting to an emergency department with chest pain or other symptoms, concerning for MI should have an electrocardiogram (ECG) performed and interpreted within 10 minutes of arrival. (7). The ECG remains the single most useful diagnostic test in cases of suspected ACS and facilitates segregation of patients into STEMI and NSTEMI pathways.(8). In NSTEMI, findings may be more variable and commonly include ST-segment depression and T-wave inversion. Criteria for acute ischemia have been validated and include ST-segment elevation of ≥ 1 mm that is concordant with the main vector of the QRS complex; ST-segment depression of ≥ 1 mm in leads V1, V2, or V3; and ST-segment elevation of ≥ 5 mm that is discordant with the main vector of the QRS complex.(9)

Serum Markers in Acute Myocardial Infarction

Damaged cardiomyocytes, release several proteins in the circulation, including myoglobin, creatine kinase (CK), and its MB isoenzyme (CK-MB), cardiac troponin (cTn) I and T, aspartate aminotransferase, and lactate dehydrogenase. The cTn biomarkers, are preferred based on superior sensitivity and specificity for cardiac injury and robust prognostic value, across the spectrum of ACS.(10-11)

Stress Hyperglycemia

Studies have shown that, an increase in glucose concentrations after admission for AMI and the overall glycemic load, after admission determine morbidity and mortality in this condition (12,13). Recent guidelines have suggested that, glucose levels should be maintained below 140 mg/dl in subjects, with STEMI (14). Because, atherothrombosis is a pro-inflammatory condition, it is important to describe the pro-inflammatory effects of glucose and the anti-inflammatory and other relevant effects of insulin, that are independent of its glucose lowering effect (15). Glucose induces reactive oxygen species generation, an increase in the expression of p47phox, as a marker of nicotinamide adenine dinucleotide phosphate oxidase, the enzyme that generates superoxide from molecular oxygen. In addition, glucose induces, an increase in nuclear factor kappa B (NF- κ B) binding, a reduction in inhibitor κ B, an increase in activating protein-1 and matrix metalloproteinases, and an increase in early growth response-1 and tissue factor (15). In STEMI, acute hyperglycemia is associated with an increase in no reflow, increased platelet aggregation, and increased left ventricular remodeling (15). Insulin, in contrast, suppresses reactive oxygen species generation, p47 phox; NF- κ B binding, early growth response-1 binding, tissue factor, and plasminogen activator inhibitor type 1 concentration (15). More recently, insulin has been shown to suppress the expression of toll-like receptors (TLR), in particular, TLR-2 and -4 (16). Both are involved in the pathogenesis of insulin resistance, whereas TLR-2 is involved in the mediation of ischemia reperfusion injury and is thus particularly relevant to patients with AMI. In addition, insulin is a vasodilator, induces nitric oxide generation and the endothelial form of nitric oxide synthase expression, and inhibits platelet aggregability, both in normal subjects and in patients, with acute coronary syndromes (15).

Effect of Stress Hyperglycaemia in Acute Myocardial Infarction

An unusually high prevalence of glucosuria, in patients without diabetes who have acute myocardial infarction was noted, as far back as 1931.(17) Since then, up to half of these patients with acute myocardial infarction have been

recognized as having raised blood glucose concentration.(18-19) Moreover, a positive association between hyperglycemia, at the time of the event and mortality from myocardial infarction has been noted.(20) Although, the mechanisms underlying this association are not fully understood, evidence that use of insulin to lower glucose concentrations decreases mortality in patients with diabetes who have myocardial infarction suggests that hyperglycaemia is not simply an epiphenomenon of the stress response mediated by cortisol nor adrenaline.(21) In patients who have had myocardial infarction, the lack of insulin associated with hyperglycaemia may lead to a decrease of glycolytic substrate for cardiac muscle and excessive free fatty acids.(21) These changes may reduce myocardial contractility at increased oxygen cost, lead to pump failure, and promote arrhythmias.(22) Consequently, hyperglycaemia at the time of myocardial infarction in patients with and without diabetes may be an important and potentially modifiable risk factor for poor outcome.(22) There is a positive association between the plasma glucose, at the time of acute myocardial infarction and mortality in patients with and without diabetes.(23) The patients, with hyperglycaemia were significantly less likely to have Thrombolysis, in myocardial infarction trial (TIMI) grade 3 (normal) flow, before PCI compared to those with normoglycemia (12 versus 28 percent, adjusted odds ratio 2.6 for the absence of reperfusion). (24) The impairment in coronary flow might reflect a prothrombotic state, or endothelial dysfunction associated with hyperglycaemia or more severe disease, lead to a greater stress response. (24)

Aims of the Study

- To study the effect of stress hyperglycemia, on the development of cardiogenic shock, heart failure, arrhythmia, and death.
- To determine, whether the site of myocardial infarction has an effect on development of stress hyperglycemia.
- To determine whether this hyperglycemia occurs, more in patients who receive thrombolytic therapy or in those who do not receive it.

PATIENTS AND METHODS

This is a prospective randomized study had enrolled 92 patient with acute myocardial infarction in Baghdad teaching hospital (Emergency department, coronary care unit and medical ward) over 1 year from the first of December 2011 to the first of December 2012.

The patients had been studied without assessment of other risk factors for Ischemic heart diseases like hypertension, obesity, smoking, dyslipidemia and family history of ischemic heart diseases.

Exclusion criteria

- Patients with history of diabetes mellitus, heart failure, chronic renal failure
- Patients receiving steroid therapy.
- Patients with previous ECG finding of LBBB.
- Patients with previous ACS.
- HbA1c > 6.5.

Full history was taken from each patient and full clinical examination was performed.

The 12 leads ECG, in addition to cardiac TroponinI (qualitative test) was done for each patient, in emergency department and repeated in CCU and medical ward.

STEMI was defined based on the criteria established by current guidelines as persistent (> 30 min) retrosternal pain associated with ST segment elevation > 0.1 mV, in two or more limb leads or > 0.2 mV in two or more pericardial leads, or acute left bundle branch block (LBBB), with biochemical evidence of myocardial necrosis (>1 positive biochemical cardiac necrosis markers measurement)(25-26).

Random plasma glucose was done for each patient, by the usual laboratory method in the emergency department, at time of admission before receiving any treatment and repeated in the second day, after hospitalization (2nd day fasting blood glucose).

Admission hyperglycemia was diagnosed, if mean random glucose level on admission was ≥ 11.1 mmol/L. Post admission hyperglycemia was diagnosed, if mean post admission fasting glucose level, calculated from glucose value on the morning after admission ≥ 7.8 mmol/L. (27-28)

HbA1C level was measured in all patients, blood draw from patient and send to Baghdad teaching Laboratories. All patients with HbA1c level $> 6.5\%$ were dropped from the study due to high probability to have undiagnosed diabetes. (29)

The patients were divided into 2 groups: g`

Group 1: normoglycemic patients (no hyperglycaemia after AMI)

Group 2: stress hyperglycaemic patients (hyperglycaemia after AMI)

Echocardiography was done to all patients, with acute myocardial infarction in coronary care unit and systolic heart failure, considered to be present if the ejection fraction is less than 40% and may manifest as regional wall motion abnormalities. (30)

The diagnosis of cardiogenic shock, depend on clinical examination like hypotension (systolic blood pressure < 90 mmHg), cold clammy skin, rapid shallow breathing, drowsiness, irritability, confusion, oliguria (urine output < 30 ml/hr) and supported, by echo cardiography. (31)

The site of myocardial infarction was recorded for each patient (lateral, inferior, anterior or extensive infarction) according to electrocardiographic reading; where a serial standard 12 lead ECG remain useful method for the detection and localization of myocardial infarction. (32)

Statistical Analysis of the Data

By using SPSS, (statistical package for social sciences) version 19 software, for windows; Data of all patients were entered and analysed. Appropriate statistical tests were performed and multiple contingency tables had been conducted. Student (t)-test, was used to find the significance of differences inbetween groups in mean age, and Chi square test was used to compare frequencies and proportions (percentages). Level of significance was set at P. value ≤ 0.05 to be considered statistically significant and highly significant, if at P. value ≤ 0.01 . Finally, the results were presented in tables and or figures.

RESULTS

There were 92 patient enrolled in this study 60 patients (40 (66.7%) males and 20 (33.3%) females) in group 1 with a mean age of (58 ± 6.3) years and the range was (42 – 83) years, and 32 patients (18 (56.25%) males and 14 (43.75%) females) in group 2 with a mean age of (60 ± 6) years and ranged (44-73) years.

No statistical significance had been found in between both groups regarding the age and genders, P. value > 0.05, table 1.

Table 1: The Demographic Features of the Patients

Demographic Variable		Group-1	Group-2	P. Value
Number		60	32	-
Age	Mean \pm SD	58 ± 6.3	60 ± 5.8	0.13 NS
	Range	42-83	44 -73	
Gender	Male NO.(%)	40 (66.7 %)	18 (56.25%)	0.44 NS
	Female No. (%)	20 (33.3 %)	14 (43,75%)	
	F:M ratio	1:2	1:1.14	

As it had been shown in table 2, The Prevalence of heart failure was significantly higher in group 2; 14 patients with heart failure out of 32 patients (43.7%) versus 8 patients out of 60 (13.3%) in group 1

Table 2: Frequency Distribution of Heart Failure among Study Groups

Heart Failure	Group-1		Group-2	
	No.	%	No.	%
Heart failure	8	13.3	14	43.7
No heart failure	52	86.7	18	56.3
Total	60	100	32	100

Odds ratio = 5.1 (95% CI (1.82 – 14.03)) P. value=0.0026

Four patients out of 60 (6%) in group-1 developed cardiogenic shock, compared to 8 patients out of 32 (25%) in group 2, p value <0.05, the prevalence of cardiogenic shock was significantly higher, in patients with stress hyperglycemia in table 3.

Table 3: Frequency Distribution of Cardiogenic Shock among Study Groups

Cardiogenic shock	Group-1		Group-2	
	NO.	%	NO.	%
Present	4	6.6	8	25.0
Absent	56	93.4	24	75.0
Total	60	100	32	100

Odds ratio = 4.7 (95% CI (1.28 – 16.9))P. value = 0.030

Table 4, show the site of myocardial infarction according to ECG findings among study groups, In group-1, there were 6 patients with inferolateral wall myocardial infarction, 14 patients with lateral wall myocardial infarction, 8 patients with inferior wall myocardial infarction, 12 patients with anterior wall myocardial infarction and 20 patients with extensive myocardial infarction, while in group-2 there were two patients with inferolateral wall myocardial infarction, 4 patients with lateral wall myocardial infarction, two patients with inferior wall myocardial infarction, 4 patients with anterior wall myocardial infarction and 20 patients with extensive myocardial infarction. So extensive MI was significantly more frequent among group 2(p=0.013)

Table 4: Frequency Distribution of Sites of MI among Study Groups

Site of MI	Group-1		Group-2		P. value
	NO.	%	NO.	%	
Inferolateral	6	10.0	2	6.2	0.82 NS
Lateral	14	23.3	4	12.5	0.33 NS
Inferior	8	13.3	2	6.2	0.49 NS
Anterior	12	20.0	4	12.5	0.14 NS
Extensive	20	33.4	20	62.6	0.013 Sig
Total	60	100	32	100	

The prevalence of arrhythmias did not significantly differ between both groups (p value > 0.05) and many different types of cardiac rhythm abnormalities were noticed, in table 5.

Table 5: Correlation of Arrhythmia to Stress Hyperglycemia

Arrhythmia	Group-1		Group-2	
	NO.	%	NO.	%
VF	6	10.0	4	12.5
VT	8	13.3	4	12.5
AF	6	10.0	6	18.8
SVT	0	0	0	0
Heart block	4	6.7	4	12.5
No arrhythmia	36	60.0	14	43.7
Total	60	100	32	100

72 patients out of 92 (78%), were subjected to thrombolytic therapy, while 20 of 92 (22%) did not received this medication.

24 patients (33%) out of 72 who received thrombolytic therapy developed stress hyperglycemia and 8 patients (40%) out of 20, who did not received thrombolytic therapy developed stress hyperglycemia

There was no significant difference in the development of stress hyperglycemia, after acute MI in relation to thrombolytic therapy (p value > 0.05) as in table 6.

Table 6: Correlation of Thrombolytic Therapy to Stress Hyperglycemia

Patients Received Thrombolytic Therapy	Group-1		Group-2		Total	
	NO.	%	NO.	%	NO.	%
Yes	48	67.0	24	33.0	72	100%
No	12	60.0	8	40.0	20	100%
Total	60	65.2	32	34.8	92	100%

P. value = 0.77 NS

The death was significantly more frequent in group -2 in comparison to group-1, there were 12 patients died out of 32 patients (37%) in group-2, versus 6 patients died out of 60 patients (10%) in group-1, P. value < 0.05 as in table 7.

Table 7: Frequency Distribution of Death among Study Groups

Death	Group-1		Group-2		Total	
	NO.	%	NO	%	NO	%
Died	6	10.0	12	37.0	18	19.60
Survive	54	90.0	20	63.0	74	80.40
Total	60	100	32	100	92	100

Odds ratio = 5.4 (95%CI (1.8 – 16.3)) P. value = 0.0038 highly significant

DISCUSSIONS

The study showed that the incidence of heart failure and cardiogenic shock were more in patients with stress hyperglycemia and this is consistent with Bellodi G. et al. (33), which showed that, hyperglycemia with acute myocardial infarction is associated with increased risk of heart failure and cardiogenic shock.

The high incidence of heart failure and cardiogenic shock can be explained by multiple reasons, including that hyperglycemia could reduce flow to the risk area (34), resulting in greater myocardial damage, before the reperfusion(35), acute increase in blood glucose level worsen endothelial function (36), therefore suggesting that, hyperglycemia induced endothelial dysfunction can also contribute to the damaging effect of hyperglycemia, during an acute myocardial infarction, acute hyperglycemia independently associated with impaired left ventricular function(37) and a large infarct size, due to an increased incidence of the no re-flow phenomenon (38).

The study showed that, patients with extensive infarction seem to develop stress hyperglycemia, more than those patients with lateral, inferior, inferolateral or anterior myocardial infarction probably, due to large infarct size in those patients, with extensive infarction this consistent with Tansey MJ. et al. (39)

This study showed that, stress hyperglycemia was not associated with an increased incidence of arrhythmia inconsistent with A. Sandaram et al.(40) showed that, hyperglycemia was associated with great incidence of conductive defect and arrhythmia. Gokhroo R. et al.(41) showed that, in acute myocardial infarction, an increased plasma glucose level have been demonstrated to be capable of inducing, such electrophysiological alterations as to favour the occurrence of arrhythmias, whose outcome could be fatal. This is consistent with the evidence that, an acute increase in blood glucose level in normal subjects produces a significant QT prolongation (42).

In this study, there were no significant differences in patients, who received thrombolytic therapy from those patients, who did not receive thrombolytic therapy, in relation to stress hyperglycemia inconsistent with Nicholas A. et al., (43) which showed that, thrombolytic therapy preserves left ventricular function and reduces mortality, after AMI.

This study, showed the incidence of death was more in patients, with stress hyperglycemia, where there were 12 patients, out of 32 patients died (37%) and this is consistent with Bolk J. et al (44) showed that, hyperglycemia is associated with increased mortality, after AMI.

CONCLUSIONS

- Stress hyperglycemia is independently a poor prognostic factor, in acute ST elevation myocardial infarction; it is independently associated with increased incidence of heart failure, cardiogenic shock and death.

- Patients with extensive myocardial infarction, are more liable to get stress hyperglycemia.
- Stress hyperglycemia is not associated, with increased incidence of cardiac arrhythmia.

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